



US009289382B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 9,289,382 B2**
(45) **Date of Patent:** ***Mar. 22, 2016**

(54) **VAGINAL INSERTED ESTRADIOL
PHARMACEUTICAL COMPOSITIONS AND
METHODS**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL
(US)

(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US);
Julia M. Amadio, Boca Raton, FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL
(US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **14/624,051**

(22) Filed: **Feb. 17, 2015**

(65) **Prior Publication Data**

US 2015/0164789 A1 Jun. 18, 2015

Related U.S. Application Data

(63) Continuation of application No. 14/521,002, filed on
Oct. 22, 2014, and a continuation-in-part of
application No. PCT/US2013/046443, filed on Jun.
18, 2013, said application No. 14/521,002 is a
continuation-in-part of application No.
PCT/US2013/023309, filed on Jan. 25, 2013, and a
continuation-in-part of application No. 13/843,362,
filed on Mar. 15, 2013, which is a continuation-in-part
of application No. 13/684,002, filed on Nov. 21, 2012,
now Pat. No. 8,633,178, said application No.
PCT/US2013/023309 is a continuation-in-part of
application No. 13/684,002, filed on Nov. 21, 2012,
now Pat. No. 8,633,178.

(60) Provisional application No. 61/932,140, filed on Jan.
27, 2014, provisional application No. 61/894,411,
filed on Oct. 22, 2013, provisional application No.
61/745,313, filed on Dec. 21, 2012, provisional
application No. 61/661,302, filed on Jun. 18, 2012,
provisional application No. 61/662,265, filed on Jun.
20, 2012.

(51) **Int. Cl.**
A61K 9/00 (2006.01)
A61K 31/565 (2006.01)
A61K 9/48 (2006.01)
A61K 47/14 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 9/0036** (2013.01); **A61K 9/4858**
(2013.01); **A61K 31/565** (2013.01); **A61K 47/14**
(2013.01)

(58) **Field of Classification Search**
CPC **A61K 9/0036**; **A61K 31/565**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies
4,093,709 A	6/1978	Choi et al.
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong

(Continued)

FOREIGN PATENT DOCUMENTS

BR	11001367-9 A2	7/2012
CN	102258455 A	11/2011

(Continued)

OTHER PUBLICATIONS

US 6,214,374, 4/2001, Schmirler et al. (withdrawn).
Abbas et al., Regression of endometrial implants treated with vitamin
D₃ in a rat model of endometriosis, *European J of Pharma*, 715 (2013)
72-75, Elsevier.
Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014,
Columbus, OH.
Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014,
Columbus, OH.
Abitec, CapmulMCM, Saffey Data Sheet, 2011, Janesville, WI.
Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014,
Columbus, OH.
Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006,
Columbus, OH.
Abitec, Excipients for the Pharmaceutical Industry—Regulatory and
Product Information, 2013, 2 pages.

(Continued)

Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend &
Stockton LLP

(57) **ABSTRACT**

According to various embodiments of this disclosure, phar-
maceutical compositions comprising solubilized estradiol are
provided. In various embodiments, such compositions are
encapsulated in soft capsules which may be vaginally inserted
for the treatment of vulvovaginal atrophy.

21 Claims, 7 Drawing Sheets